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Successful Improvement of Frequency and Symptoms of Premature Complexes after Oral Magnesium Administration

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Abstract

Background: Premature ventricular and supraventricular complexes (PVC and PsVC) are frequent and often symptomatic. The magnesium (Mg) ion plays a role in the physiology of cell membranes and cardiac rhythm.

Objective:We evaluated whether the administration of Mg Pidolate (MgP) in patients with PVC and PsVC is superior to placebo (P) in improving symptoms and arrhythmia frequency.

Methods: Randomized double-blind study with 60 consecutive symptomatic patients with more than 240 PVC or PsVC/h on 24-hour Holter monitoring who were selected to receive placebo (P) or MgP. To evaluate symptom improvement, a categorical and a specific questionnaire for symptoms related to PVC and PsVC was made. Improvement in premature complex density (PCD) per hour was considered significant if percentage reduction was ≥70% after treatment. The dose of MgP was 3.0 g/day for 30 days, equivalent to 260mg of Mg element. Any patient had structural heart disease or renal failure.

Results: Of the 60 patients, 33 were female (55%). Ages ranged from 16 to 70 years old. In the MgP group, 76.6% of patients had a PCD reduction >70%, 10% of them >50% and only 13.4% <50%. In the P group, 40% showed slight improvement, <30%, in the PC frequency ($p < 0.001$). Symptom improvement was achieved in 93.3% of patients in the MgP group, compared with only 16.7% in the P group ($p < 0.001$).

Conclusion: Oral Mg supplementation decreases PCD, resulting in symptom improvement. (Arq Bras Cardiol. 2012; [online].ahead print, PP.0-0)

Keywords: Arrhythmias, cardiac; ventricular premature complexes; magnesium; ion channels.

Introduction

Premature ventricular and supraventricular complexes (PVC and PsVC) are frequent and often symptomatic. Their prevalence can occur in up to 50% of the general population, especially[1]. The incidence of this arrhythmia increases with age[2-4]. The studies show that most of these patients had <1 PVC per hour, usually monomorphic and single forms[2,3].

Symptoms related to PVC and PsVC can be very troublesome or even disabling. Patients may refer to these symptoms as a "skipped beat," "punch in the chest," palpitations, dyspnea, cough, dizziness, atypical chest pain, and near syncope[5,6], affecting quality of life. These symptoms are usually noticed when the PCD is high. Premature complexes are directly related to heart cell excitability, which is influenced by electrolyte balance in intracellular fluid. The interaction between magnesium (Mg) and calcium (Ca) has particular relevance in the regulation of nerve and muscle cell permeability[7-9], and in the ATPase – Na +/K + pump[8,9]. By acting on the physiology of cell membranes, Mg has a special role in cardiac rhythm maintenance[8,9].

Mg is the second most abundant intracellular cation[8,9] and plays an important role in the activity of many coenzymes and ATP-dependent reactions, including membrane-dependent energy transport[9,10]. Less than1% of magnesium is found in blood[9] and only approximately 0.3% in serum[11,12]. Therefore, the intracellular deficiencies can be underdiagnosed[8].

Lifestyles characterized by stress, low micronutrient intake, physical training, sleep deprivation, and the use of certain medications (diuretics, aminoglycosides, and cyclosporine) may lead to Mg deficiency. This ion is mainly found in seeds, nuts, vegetables, and wheat bran. In the general population, magnesium deficiency probably occurs due to low magnesium dietary intake[13,14] ,that needs to maintain adequate intracellular values and, in the elderly, by decreasing appetite[14].

This study aimed to assess whether oral administration of magnesium pidolate (MgP) in patients with PVC or PsVC is superior to placebo in improving symptoms and frequency of PC, as well as whether symptom improvement is related to a significant reduction in arrhythmia frequency.

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Methods

Study Design and Participants

Patients were recruited from the Arrhythmia Unit of the Heart Institute (InCor), University of São Paulo Medical School and Core Vita Clinics. Patients were eligible if they were symptomatic and had more than 240 PVC or PsVC per day on 24h Holter monitoring(or more than 10/hour). Exclusion criteria were impaired renal function, structural heart disease (except mitral valve prolapse without regurgitation), or the use of concomitant drugs. The study was approved by the ethics committees of the participating centers in the study with the number CAPPesq-0613/10.

Procedures

After providing written informed consent, all trial participants were randomly assigned to receive placebo (P) or magnesium pidolate (MgP), each administered in a blinded manner. All the patients did echocardiogram and none of them had structural heart disease or electrolyte disturbances; the determination of electrolytes(magnesium, sodium, calcium and potassium) and the renal function were normal.

The dose of the MgP was 3.0 g/day for 30 days, which contains 260mg of Mg element. The magnesium, sodium, calcium, and potassium serum dosage was taken at baseline, at 15 days, and at 30 days after randomization.

Holter

The 24-hour Holter (3 channels) was performed at baseline and 30 days after the medication use. The count of the premature complexes was performed following the institution protocol and the premature complex density (PCD) was performed dividing the total number of atrial and ventricular extra systoles Holter counted in the number of hours of recording.

Outcomes

Follow-up visits occurred at randomization, after 15 days, and after 30 days.

To evaluate symptom improvement, a specific questionnaire related to PC was made with the following questions:1- Failure or "leaps" in the chest ;2-Couch with palpitations;3-Dizziness;4-Dyspnea:5-Sudoresis and/or chest pain. According to frequency of symptoms was made a "score" (Fig. 1). For this "score", was only considered an improvement, if the patient had a reduction of at least two categories, for example, was in the score IV before treatment and migrated to the score I or II after treatment .Furthermore, it was made a categorical classification of patients with questioning whether there was improvement of symptoms, with only answers "yes" or "no ".

Statistical Analysis

To meet the objectives of the study, we calculated the percentage changes in PCD /hour, and was considered success criteria, after treatment, the percentage reduction ≥70% per 24-hour Holter. Data are presented using summary statistics (mean, standard deviation, median, minimum, maximum). Outcome variables were compared between groups using a Mann-Whitney test[15]. The improvement of either PCD or symptoms was described using absolute and relative values. The existence of an association between groups and the improvement of each criterion was performed using Fisher's exact test[15]. A p value of 0.05 was considered statistically significant. We described the values of magnesium and potassium before medication, and at 15 and 31 days after medication use, according to groups, and also compared the values between groups and moments using analysis of variance with repeated measures and 2 factors[16].

A statistical power of 80% was chosen to detect a 60% symptom reduction with MgP and 30% with P, with a confidence interval of 95%.

Results

A total of 60 patients were enrolled in the program between October 2010 and August 2011. Both treatment groups had similar baseline characteristics. The mean age was 46.47 (MgP) to 48.53 (P), and 55% were women (Table 1). Age description and PCD variation according to each group are described in Table 1.The average extra-systole in 24 hours in both groups was higher than 4.955 PC/day. Twelve patients had mitral valve prolapse without insufficiency (5 in group P and 7 in group MgP).

Quiz

Symptom	Points
Failures or "leaps" in the chest	
Couch with palpitation	
Dizziness	
Dyspnea	
Sudoresis and/or chest pain	
Total	

Points
A - never - 0 point
B - once to 5 times/day - point
C - 6 to 20 times/day - 2 points
D - ≥ 21 times/day - 3 points

"Quality of Life" Score
Symptom Classification
I - Asymptomatic - 0 point
II - Mid Symptomatic - 01 a 05 points
III - Moderate Symptomatic - 06 a 11 points
IV - Severe Symptomatic - more than 12 points

Figure1 - *This figure shows the score system to assess improvement of symptoms before and after the drugs in both groups (placebo and magnesium pidolate).*

Frequency of Premature Complexes

In the MgP group, 76.6% of patients had a PCD reduction >70%, 10% of them >50% and only 13.4% <50%. In the P group, 40% showed slight improvement, <30%, in the PC frequency (Table 2/ Figure 2). Patients in the MgP group had an average reduction of 77.13% (SD = 24.57%) of PCD, whereas the placebo group had an average increase of 47.99% (SD = 158.93%) in PCD (p<0.001) (Table 2/Figure 3). This difference was also consistent for both PVC and PsVC (p<0.001) (Table 2). A few patients (13.4%) had only a slight improvement in PC density in the MgP group (<50% in PC frequency), but had improvement in symptoms.

Symptoms

In the P group, only 16.7% reported symptom improvement (score), whereas in the MgP group there was an improvement of 93.3% (p <0.001) (Table 2). As a categorical variable, there was improvement of symptoms in 93.3% of patients in the PMg, compared with only 13.3% in the placebo group (p <0.001) (Table 2). Figures 4 and 5 show the superiority of symptom improvement in patients receiving MgP compared with patients receiving P.

Laboratory Findings

There were no significant changes in serum magnesium, potassium, sodium and calcium during the study in both groups. Serum magnesium did not differ significantly between groups (p = 0.743) or between periods of time (before and after oral supplementation; p = 0.154); moreover, serum potassium did not differ statistically between groups or during follow-up (p = 0.415, p = 0.804, respectively). Table 2 and Figure 6 illustrate the changes in magnesium.

Study Discontinuation and Adverse Events

Only one patient in the MgP group had to discontinue the protocol after 10 days due to diarrhea, which was promptly resolved within 24 hours.

Discussion

Oral magnesium supplementation not only decreases the density of premature ventricular and supraventricular complexes, but also improves symptoms compared to placebo. In the placebo group, only 16.7% showed improvement in symptoms compared to 93.3% of patients using MgP. Although most patients have improved PC density and symptoms, some patients have improved symptoms without a significant drop in PC density. The worsening of PCD in some patients in the placebo group can perhaps be explained by the great variability that involves spontaneous idiopathic arrhythmias. However, it is important to note that both groups were subjected to this variability, and even then, there was a statistically significant reduction of PCD in the magnesium group compared with the placebo group.

The mechanisms by which magnesium administration reduces the incidence of PC are not entirely known. Magnesium is regarded as a significant regulator of cardiac cell function. Depletion of magnesium, as shown in some studies, may be proarrhythmic[14]. Zehender et al[17] demonstrated that increased intake of potassium and magnesium in patients with frequent ventricular arrhythmias can result in a moderate but significant antiarrhythmic effect, although the frequency of tachyarrhythmia and symptoms has not been changed[17]. However, this sample differs from our results, probably because the population is different: most patients had other cardiac co morbidities, and some were using other medications.

On the possibility of oral magnesium overload, it is important to note that patients in the MgP group had a normal Mg serum dosage during the 30-day follow-up, without major adverse effects or the need for suspension (except for a single patient with diarrhea). It is likely that intracellular levels of Mg are low, despite normal serum dosage, since serum dosage corresponds to only 0.3% of total magnesium. It would be interesting to find out minimally invasive, accurate methods to detect intracellular Mg levels[18] to better understand many diseases, including cardiac arrhythmias.

There are some studies with fluorescent markers specific to magnesium (and Mg-Fluo-4/AM KMG-20/AM)[19], that aim at the cation dosage in various cell types, such as platelets, red blood cells, lymphocytes[12], cardiomyocytes (in rats)[19] and epithelial sublingual cells[18]. Silver et al[18] showed a significant correlation between the magnesium values in heart muscle biopsies from bypass surgery, with the values measured in sublingual epithelial cell smear. Moreover,

Table 1 - Baseline Characteristics of Study Patients

Characteristic	MgP	Placebo	p value
Gender Female, n (%)	17 (56,7%)	16 (53,3%)	0,795
Age (SD) #	46,47 ± 17,42	48,53 ± 13,18	0,606
Valve Mitral Prolapses (SD)	07 (23,3%)	05 (16,7%)	0,519
PCD*	256,41± 294,56	206,46 ± 249,89	0,496
PVC density	129,31 ± 219,13	90,90 ± 157,72	0,639
PsVC density	126,83 ± 225,82	115,55 ± 242,03	0,066
Magnesium	2,05 ± 0,13	2,08 ± 0,14	0,439
Potassium	4,20 ± 0,36	4,23 ± 0,36	0,690

**Density of PC, PVC, PsVC: premature complexe per hour; # - Standard Deviation.*

Table 2 - Clinical Outcomes at 30 Days.

Variable	PMg	Placebo	p
Improvement of PCD, n (%)			< 0.001
< 0%	0 (0.0%)	18 (60%)	
0 to 30%	2 (6.7%)	12 (40%)	
30 to 50%	2 (6.7%)	0 (0.0%)	
50 to 70%	3 (10.0%)	0 (0.0%)	
70% or more	23 (76.6%)	0 (0.0%)	
Improvement of symptoms, n (%)			< 0.001
No	2 (6.7%)	26 (86.7%)	
Yes	28 (93.3%)	4 (13.3%)	
Improvement of score, n (%)			< 0.001
Less than 2 points	2 (6.7%)	25 (83.3%)	
Two points or more	28 (93.3%)	5 (16.7%)	
Reduction of PCD, % (SD)	77.13 ± 24.57	-47.99 ± 158.93	< 0.001
Reduction of PVC*	31.83 ± 280.62	-40.78 ± 187.34	< 0.001
Reduction of PsVC	22.64 ± 223.05	-212.78 ± 732.13	< 0.001
Magnesium (SD)	2.09 ± 0.10	2.09 ± 0.12	< 0.743
Potassium (SD)	4.17 ± 0.27	4.26 ± 0.29	< 0.415

**Density of PC, PVC, PsVC: premature complexe per hour.*

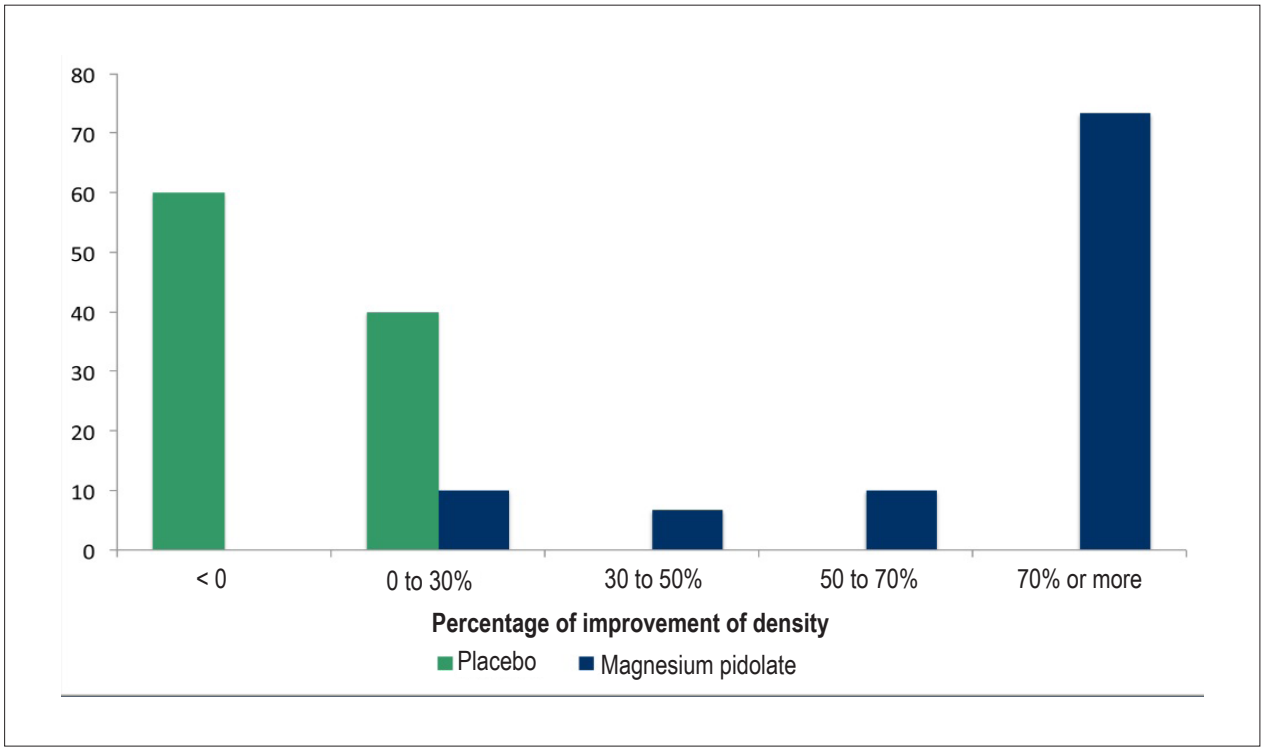

Fig. 2 - *Distribution of patients according to the percentage of improvement in the density of ventricular premature beats after 30 days in the placebo group (green) and magnesium pidolate (blue).*

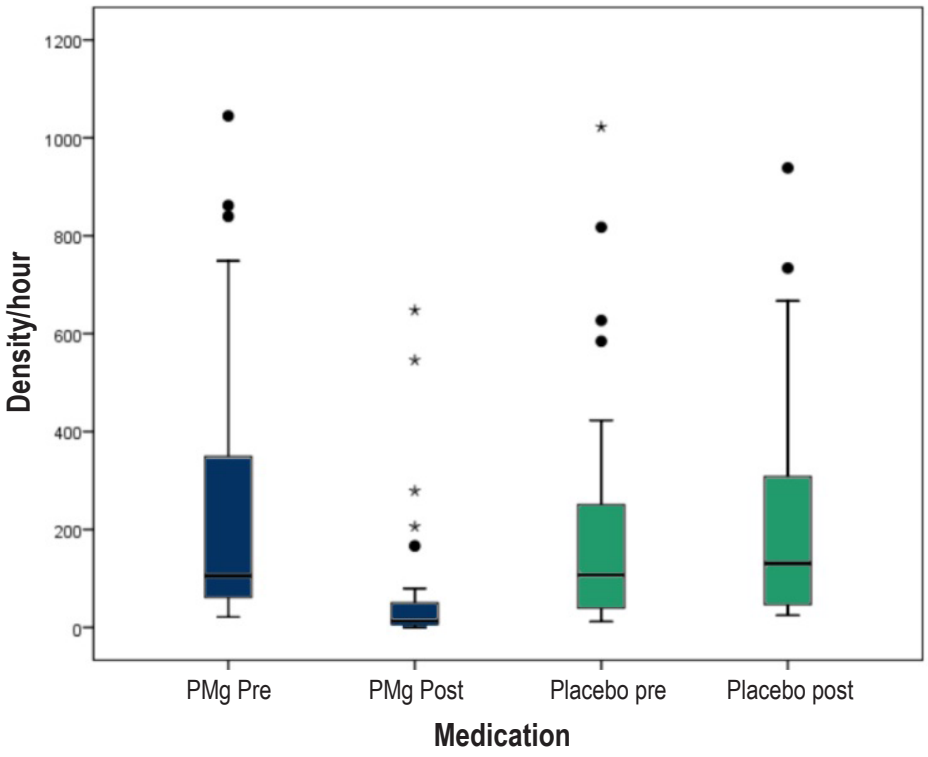

Figure 3 - *Box-plot of the density of ventricular premature beats per time, before and after the treatment, according to each group: magnesium pidolate (blue) and placebo (green).*

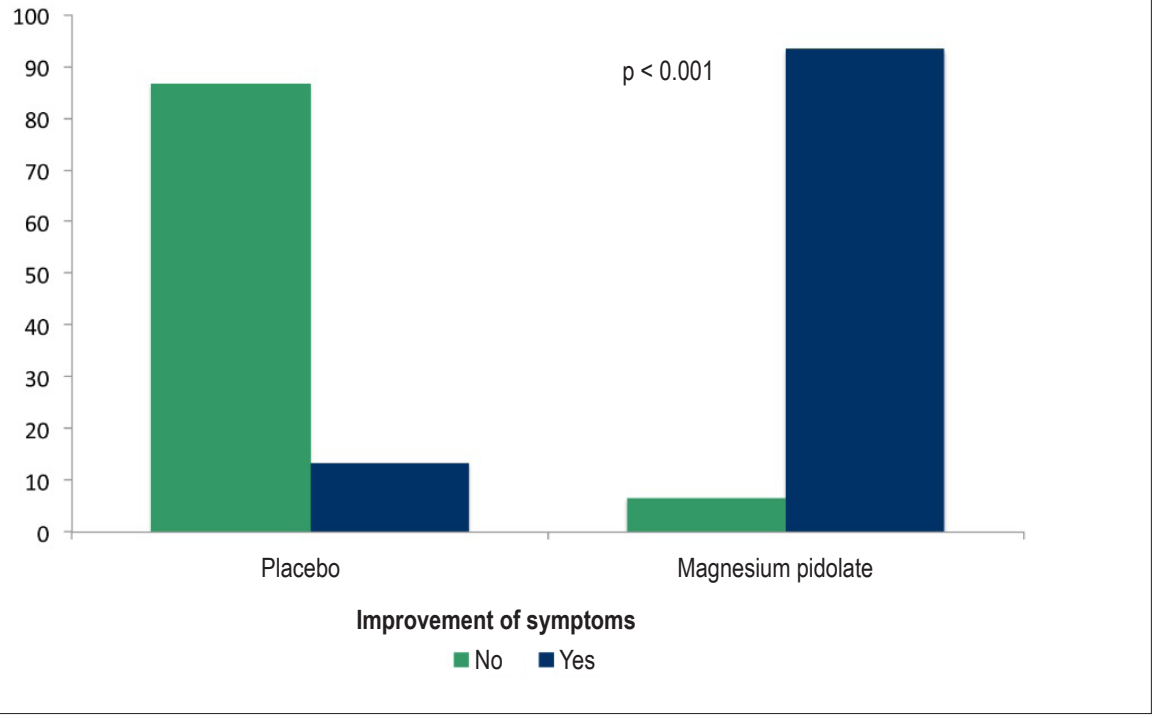

Figure 4 - *Percentage of patients who presented improvement of the symptoms: Yes (blue) or No (green), according to the group of treatment.*

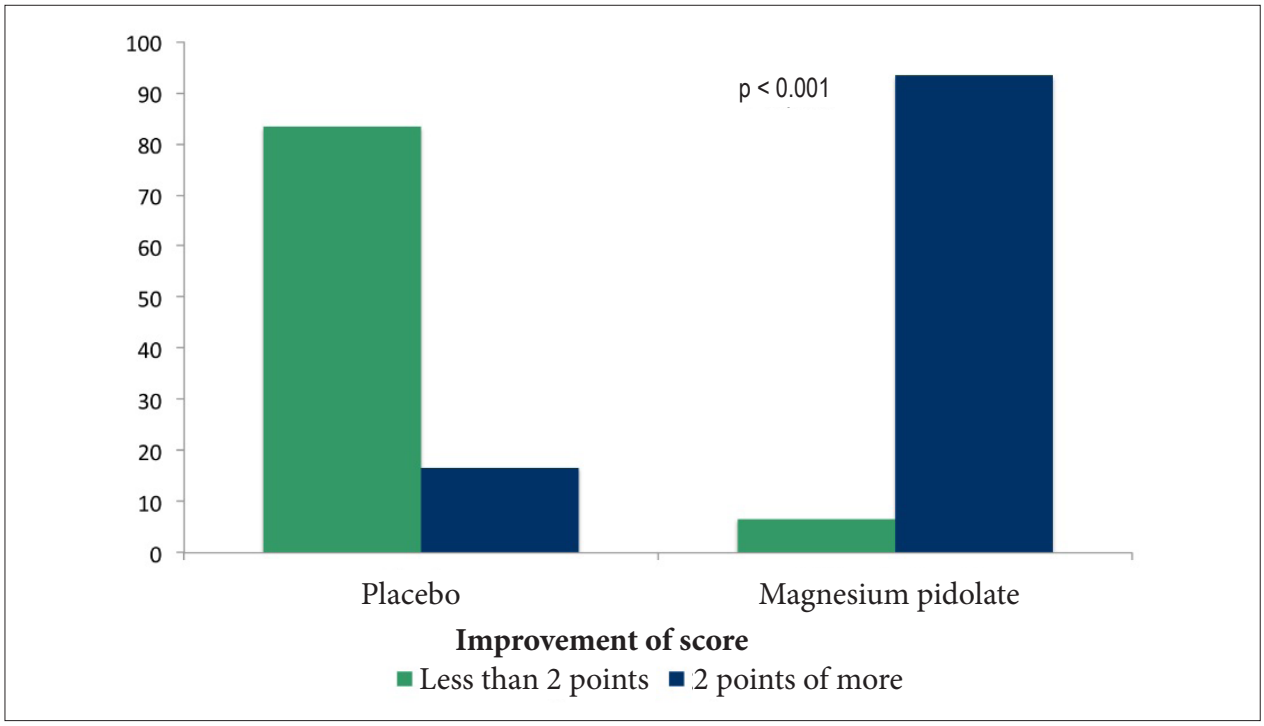

Figure 5 - *Percentage of patients who presented improvement in the score of symptoms. Smaller than 02 points (green) and greater than 02 points (blue).*

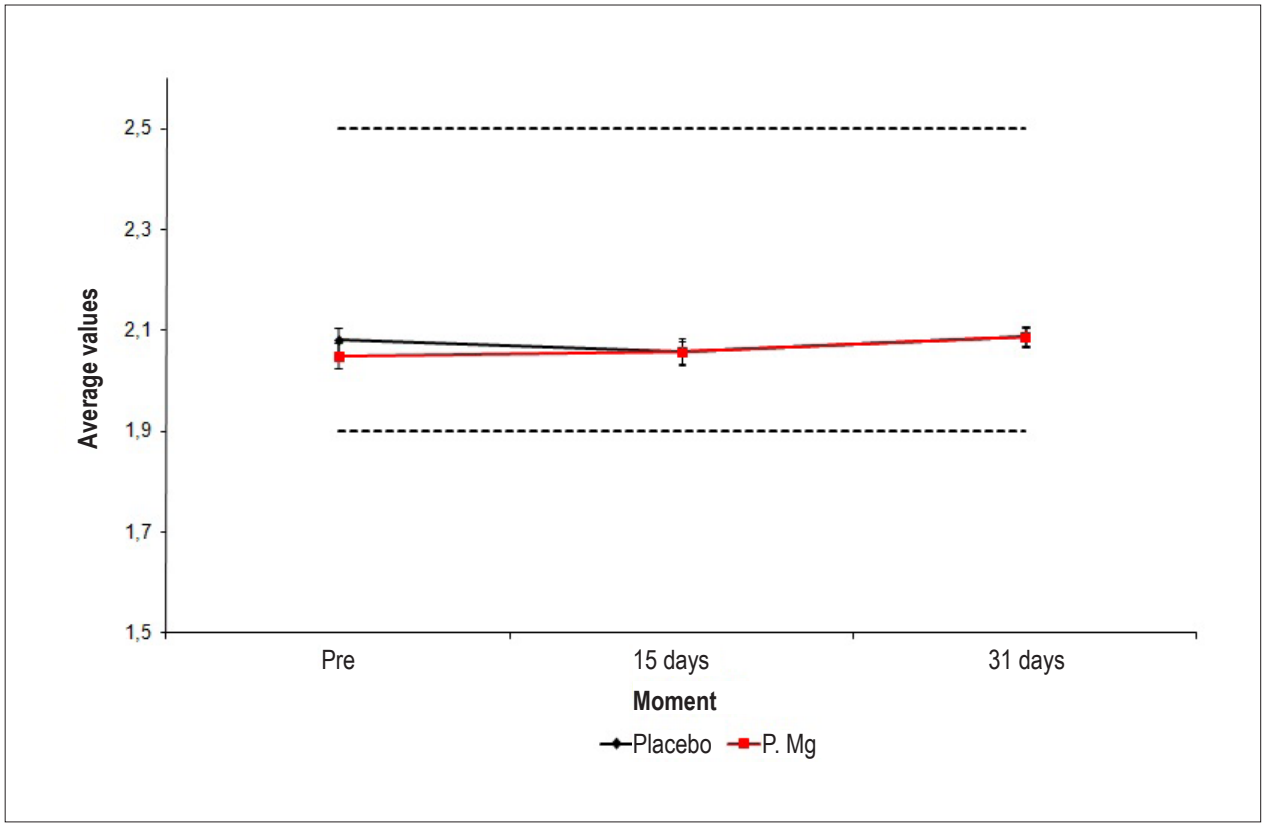

Figure 6 - *Serum levels of magnesium before and on the 15th and 30th day of treatment with placebo (black line) and magnesium pidolate (red line).*

magnetic resonance imaging (MRI) is a noninvasive test for tissue Mg analysis. Recently, the Transient Receptor Potential Melastation channel and its role in hypomagnesemia were identified. Chronic Mg deficiency may be explained by changes in these specific membrane transporters[12,20,21].

Magnesium is closely related to the maintenance of cellular ionic balance in combination with sodium, potassium, and calcium; it cooperates with the Na^+/K^+ ATPase pump[8,9,14]. Magnesium deficiency causes an increase in intracellular Na^+, which allows cellular K^+ loss[9]. Mg also affects calcium homeostasis, and many calcium channels are magnesium dependent. In addition, Mg is needed for the release and action of parathyroid hormone[9].

Some conditions are associated with magnesium deficiency, such as metabolic syndrome[22,23], hypertension, congestive heart failure, diabetes, preeclampsia, and arrhythmias[14]. A single study showed that 365 mg of magnesium per day for 8 weeks lowers blood pressure[24]. According to Tong and Rude, magnesium reduces irregular heartbeat, and because intracellular Mg depletion may be present despite a normal serum Mg, magnesium deficiency must always be considered as a potential factor in cardiac dysrhythmias[25]. In the intensive care unit, magnesium is used when arrhythmias do not respond to conventional medications, and also in digitalis intoxication[26]. In heart failure, magnesium deficiency is caused by diuretic therapy, which increases the incidence of arrhythmia, among them premature complexes[8,14].

The Mg balance among different compartments of the body occurs slowly, so that the concentration of Mg in one tissue does not correspond to that in another[12]. Less than 1% of total body Mg is present in blood[9] and only 0.3% in serum[11,12], so serum levels do not reflect the total body stores[27,28]. Therefore, even without changes in magnesium serum level, there was an improvement in arrhythmia with Mg replacement. It would be interesting to evaluate the nutritional value of Mg in food after processing (refining) and to establish the necessary amount of intake correlated with the values of intracellular Mg.

Although symptom improvement could be associated with a reduction in PC density, even in some cases in which this decline is not significant, symptoms also improved. This is partly explained by the placebo effect, as well as magnesium action in nerve cells. A nutrition education rich in magnesium may be a practical alternative for the treatment of this arrhythmia. However, this information must be evaluated in another study. It is also important to control serum Mg during treatment and to assess renal function.

Limitations

Long-term follow-up was not performed; therefore, it is not possible to establish whether these patients are free from symptom recurrence after oral replacement of magnesium. Intracellular magnesium was not measured, but Mg serum dosages have shown that this replacement was safe and effective. The goal of reduction in the density of premature ventricular and supraventricular complexes and symptom improvement was achieved. The specific symptom score was not validated, because it does not exist in the literature. However, a simple categorical score was also made, with a good correlation between reduced PCD and symptom improvement. Moreover, the aim of this study was not to prevent life threatening arrhythmic events. It shows that the data should not be used as justification for treating patients with this objective, especially those with heart disease.

Conclusion

Simple oral Mg replacement reduced the density of premature ventricular and supraventricular complexes and specially improved symptoms in our study population (no cardiac heart disease).Clinical and molecular studies are needed to evaluate intracellular Mg and develop better targets for the daily needs of this ion, show probable deficiencies, and explain how to prevent and better treat patients with symptomatic premature ventricular and supraventricular complexes and no apparent heart disease.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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